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REVIEW

Reversal and Remission of T2DM – An Update for Practitioners

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Abstract: Over the past 50 years, many countries around the world have faced an unchecked pandemic of obesity and type 2 diabetes (T2DM). As best practice treatment of T2DM has done very little to check its growth, the pandemic of diabesity now threatens to make health-care systems economically more difficult for governments and individuals to manage within their budgets. The conventional view has been that T2DM is irreversible and progressive. However, in 2016, the World Health Organization (WHO) global report on diabetes added for the first time a section on diabetes reversal and acknowledged that it could be achieved through a number of therapeutic approaches. Many studies indicate that diabetes reversal, and possibly even long-term remission, is achievable, belying the conventional view. However, T2DM reversal is not yet a standardized area of practice and some questions remain about long-term outcomes. Diabetes reversal through diet is not articulated or discussed as a first-line target (or even goal) of treatment by any internationally recognized guidelines, which are mostly silent on the topic beyond encouraging lifestyle interventions in general. This review paper examines all the sustainable, practical, and scalable approaches to T2DM reversal, highlighting the evidence base, and serves as an interim update for practitioners looking to fill the practical knowledge gap on this topic in conventional diabetes guidelines.

Keywords: weight loss, very low energy, very low calorie, bariatric surgery, orlistat, electrical muscle stimulation, low carbohydrate, behaviour change, diabetes reversal, diabetes remission

Introduction: The Ever-Growing Pandemic of T2DM

Type 2 diabetes mellitus (T2DM) is a complex, multifactorial, metabolic disease provoked by chronic overconsumption of unhealthy calories in those with a sedentary lifestyle and genetic predisposition, although no specific important risk gene(s) has been identified yet. It is preceded by a variable period of pre-diabetes during which time the body tries to compensate for blood glucose level spikes coinciding with increasing insulin resistance and attenuation of insulin production, but which ultimately progresses if the diet is left unchecked, resulting in a chronic state of elevated blood glucose level. Combined with increasingly sedentary lifestyles, T2DM is on course to be the largest non-communicable pandemic in human history. It has been estimated that the world prevalence of diabetes among adults (aged 20–79 years) in 2010 was 6.4%, affecting 285 million people, and this is projected to increase to 7.7%, or approximately 642 million adults, by 2030.[1] Although the prevalence of T2DM is higher in developed than in developing countries,[2,3] between 2010 and 2030, there is expected to be a 69% increase in the number of adults with diabetes in the developing world compared to a 20% increase in the West.[4]

Since the advent of processed food in the 1950s, unhealthy constituents (refined sugars and saturated fats) have increasingly become the dominant part of total calorie intake in the developed world, whilst consumption of natural fibres from organic, fresh whole foods has fallen. The calorie-dense, widely available, and addictive menus touted to a poorly informed public have no doubt played a part in an obesity pandemic – facilitated by underlying epigenetic and genetic

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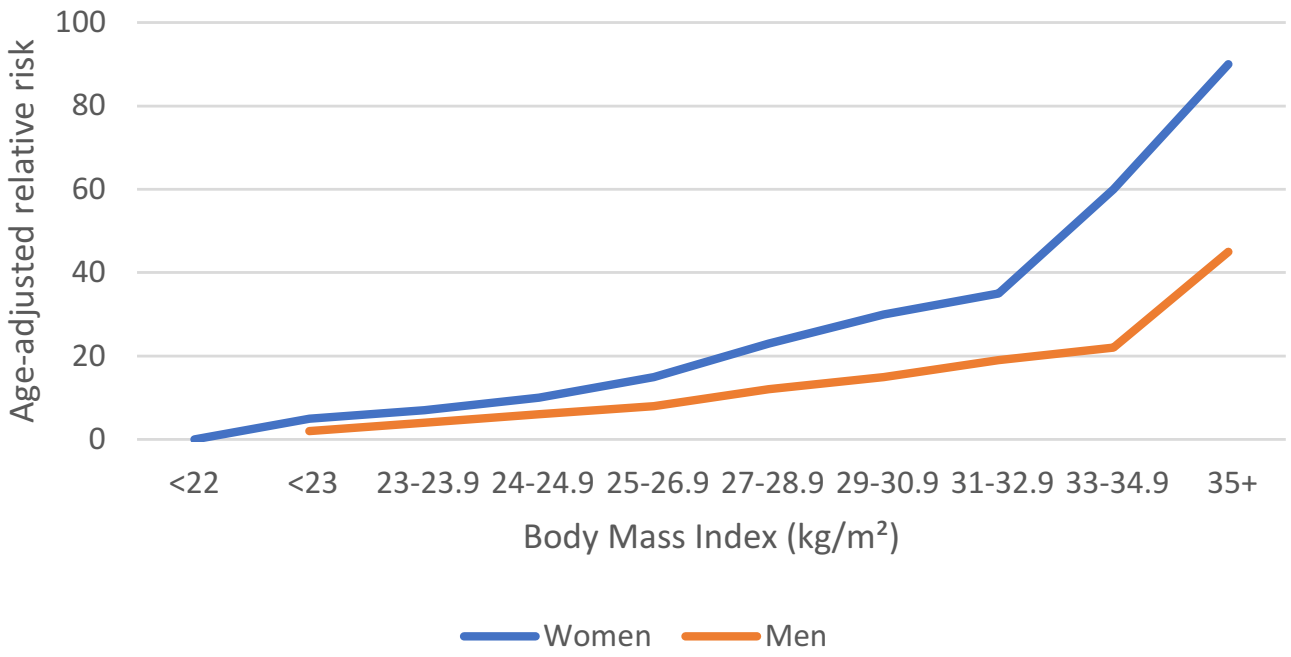

Figure 1 BMI and risk of diabetes rise in lockstep.
Note: Data from Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care*. 1994;(9):961–969.[6]

factors that are common. As Figure 1 reveals, the T2DM pandemic appears to be preceded by, and then moves in lockstep with, an underlying obesity pandemic.[5,6]

The annual cost of diabetes in the US has been estimated to have risen from US $245 billion in 2012 to US $327 billion in 2017 – that is a 33% increase, in just five years.[7] For the UK, the costs of diabetes to the National Health Service (NHS) have also risen, reaching a staggering US $15 billion in 2017. Some 80% of the cost of diabetes is spent on treating complications.[8] Successful reversal of T2DM would relieve health-care systems and societies around the world from a substantial, and increasingly unsustainable socio-economic burden.[9] This review paper gives the practitioner an update about the reversibility of T2DM, which is still an emerging area of practice.

Can T2DM Really Be Reversed?

T2DM has long been regarded as a chronic, irreversible illness, requiring a continuous titration of add-on pharmacotherapy, and which inexorably progresses in over 50% of patients to insulin dependence within 9–10 years.[10] However, many studies and reports have emerged that challenge that narrative with new approaches to managing the disease which prioritize reversal and remission.[11,12] Respected organizations like the World Health Organization and Diabetes UK now openly acknowledge that diabetes is metabolically reversible – at least for a period of time. Four approaches are detailed on the Diabetes UK website: low carbohydrate diets, very low-calorie diets, exercise, and bariatric surgery.[13,14]

As a result of the debate around and interest in diabetes remission, a joint consensus statement has emerged around the definition of diabetes remission from the American Diabetes Association (ADA), the Endocrine Society, the European Association for the Study of Diabetes (EASD) and Diabetes UK. The consensus position now defines remission as being a return to below the World Health Organization (WHO)/American Diabetes Association (ADA) original diagnostic thresholds for diabetes and this return should be maintained for 3 months without any glucose-lowering pharmacotherapy (see Table 1). Measurement of either HbA1c or blood glucose can be used to confirm remission. Patients in remission should thereafter be kept under regular review with annual testing as a minimum. It is important to note that the term “cure” has not been applied to T2DM, as weight regain is always a risk factor for its re-occurrence.[15] Although the terms “reversal” and “remission” are used interchangeably, recent consensus supports the use

Table 1 Published Criteria for T2DM in Remission[15]

	Criteria for Remission	Confirmation
ADA, Endocrine Society, EASD, and Diabetes UK joint consensus statement on the definition of T2DM remission[15]	**Complete remission (no longer having prediabetes):** HbA1c< 6.5% (<48 mmol/mol) or fasting blood glucose <7 mmol/L, or estimated HbA1c less than 6.5% calculated from continuous glucose monitoring values; maintained without anti-diabetes drugs for at least 3 months. Testing of HbA1c to document a remission should be performed just prior to an intervention and no sooner than three months after initiation of the intervention or withdrawal of any glucose-lowering pharmacotherapy.	Reviewed annually as a minimum

of "remission" in the context of T2DM. Furthermore, a distinction could be made between mere reversal (return to normoglycaemia) and true remission (normoglycaemia maintained for at least 3 months in the absence of glucose-lowering drugs).[16]

Surgical Reversal and Remission of T2DM

It has been known for over 30 years that bariatric surgery can reverse T2DM and change outcomes for obese patients with T2DM.[12] Systematic reviews showed that bariatric surgery could initially reverse T2DM for 58% to 95% of patients.[17–20]

In one long-term study, T2DM patients who had undergone bariatric surgery had a reversal rate of over 51% at 12 years, with an average of 35kg weight loss, representing a reduction of 26.9% weight from baseline. The long-term studies of bariatric surgery have been usually in a group of patients who have BMIs of 35 or more.[21,22] Another long-term prospective study of outcomes after bariatric surgery reported a 10-year remission rate from T2DM of just 36%.[23] Long-term outcomes from bariatric surgery of course depend on multiple factors, including type of surgery, patient baseline co-morbidities, patient willingness to engage with lifelong lifestyle change, and the quality of ongoing surveillance. Whilst these studies are encouraging, more long-term studies are required to be certain about the true outcomes of glucose homeostasis after bariatric surgery. Initial data suggested that gastric bypass is the most effective at inducing diabetes remission in T2DM patients, followed by sleeve gastrectomy, and then gastric banding.[24] Longer term data (5-year) reveal that remission rates for T2DM patients after sleeve gastrectomy are nearly as good as those for gastric bypass.[25,26] Laparoscopic gastric banding and gastric balloons are often adjuncts to weight loss, and have good short-term results in type 2 diabetes, however data on their long-term impact on T2DM are scant. Recently "pill balloons" which do not require any procedure have become available.[27]

In diabetic obese adolescents who have had bariatric surgery, the remission rate of T2DM after the surgery was 82% (95% CI: 66–94%) for the first year, 82% (95% CI: 60–98%) for the second year, 98% (95% CI: 83–100%) for the third year, and 99% (95% CI: 82–100%) >5 years after surgery. Other long-term data suggest remission rates settling at around 85% at 5 years.[28,29] Interestingly, after gastric bypass surgery, one study with 5 years of data suggested that adolescents appear to have similar weight loss to adults but do better than adults when it comes to remission of T2DM. However, this advantage comes at the possibly unacceptable cost of a high rate of abdominal re-operations and nutritional deficiencies in the adolescent group.[30,31] These undesirable side effects have led some to question whether adolescents should wait until they are adults before undergoing bariatric surgery.[32]

More than 25% of T2DM patients require insulin. Those already on insulin have a lower diabetes remission rate after bariatric surgery than those on oral hypoglycemics only. In those T2DM patients already on insulin, 62% who underwent gastric bypass were off insulin at 12 months. Gastric bypass was a weight-independent predictor of insulin therapy cessation early after surgery, even before significant weight loss.[33] Thus, the beneficial effects of surgical intervention could not be entirely due to weight loss alone, and the metabolic nature of the surgery itself was likely also playing an, as yet, poorly understood part.[34]

It was only in 2016 that the second Diabetes Surgery Summit produced recommendations, endorsed by 45 national medical societies worldwide, to use bariatric surgery as a treatment for T2DM in adults with body mass index >40, or >35 kg/m^2 in those with obesity-related co-morbidities.[35] These guidelines were based on the observation that there was uniform improvement in glycemic control after any bariatric operation.[36] In addition to early and dramatic post-operative improvement in glycaemia and insulin sensitivity, bariatric surgery causes alterations in gastrointestinal hormone release, including ghrelin, leptin, cholecystokinin, peptide YY, and in particular, glucagon-like peptide 1 (GLP-1), which may correct feeding behavior via the gut-brain axis in addition to sustaining euglycaemia.[37] Studies have shown that postprandial levels of endogenous GLP-1 after bariatric surgery can be 10 to 20 times higher compared with before surgery.[38]

Interestingly, bariatric surgery has been associated with dramatic changes in the gut microbiome, with reversion from an "obesogenic" to a "lean" profile.[39–44] The exact neuroendocrine mechanisms by which bariatric surgery effects all these improvements in glycemic profile are not yet fully understood, although it appears that a combination of sudden, sharp energy reduction,[45] changes in vagal tone,[46] gut hormones in particular GLP-1,[47] bile acid metabolism,[48] reprogramming of intestinal glucose metabolism and the colonic microbiome[49] have all been implicated.

Like all surgeries, there is a risk of complications, although this is small in bariatric surgery. In randomized clinical trials, the mortality rate within 30 days was 0.08% (95% CI, 0.01–0.24%) and the mortality rate after 30 days was 0.31% (95% CI, 0.01–0.75%). The complication rate was 17% (95% CI, 11–23%), and the reoperation rate was 7% (95% CI, 3–12%).[50] Patients who require reoperation for either revision or complete reversal of their initial bariatric surgery have further attendant risk, the magnitude of which is still under investigation. Individually, rates of major adverse events in the first 30 days were 5.0% for roux-en-y gastric bypass (RYGB), 2.6% for sleeve gastrectomy, and 2.9% for laparoscopic adjustable gastric banding (LAGB).[51] Significant complications include anastomotic leak or hemorrhage, dumping syndrome, worsening acid reflux, marginal ulceration, and micronutrient deficiencies.[52–56] For each patient, these risks must be weighed up against the risks associated with leaving their morbid obesity untreated. Interestingly, recent studies have shown that bariatric surgery for T2DM is of benefit even to lower BMI groups.[57] In non-obese (BMI <30) type 2 diabetes, remission rates for bariatric surgery have been reported to range from 13.3% to 90.2%, depending on the type of procedure, with the longest study having a three-year follow-up.[58–60]

Even after remission following surgical intervention, T2DM patients can still relapse. The prospective Swedish Obese Subjects study reported remission rates of T2DM at 2, 10 and 15 years of follow-up as 72.3%, 38.1% and 30.4%, respectively.[61] These results were mirrored in a retrospective cohort study including 4434 obese patients with diabetes who underwent gastric bypass. The average remission time after bypass was 8.3 years, with 35.1% suffering from T2DM relapse by year 5.[62] Revisional bariatric surgery has been shown to have utility for recurrent metabolic disease, especially T2DM. Depending on the index surgery and subsequent reconstruction, improvement of diabetes was seen in 65–100% of patients. Gazda et al[63] retrospectively studied the use of GLP-1 receptor agonist-based weight-loss programs for recidivism after bariatric surgery as an alternative to revisional surgery. They found that GLP-1-based programs to be superior to non-GLP-1 programs and intensive lifestyle modification alone for treating post-bariatric surgery weight regain, regardless of surgery type.

Further mechanistic research and much larger prospective randomized studies would be needed to identify the optimal treatment strategies for post-bariatric weight regain and relapse of T2DM with residual or recurrent metabolic disease.[64]

Predicting Remission Outcomes After Surgery

With an increasing quantity of data available for analysis, a long list of pre-operative clinical and biochemical factors has been identified as being potentially predictive of T2DM remission and relapse after bariatric surgery, including the surgical procedure, insulin sensitivity, weight regain, bile acids, changes of gut microbiota, gastrointestinal hormones, particularly ghrelin, glucagon-like-peptide-1, gastric inhibitory polypeptide and peptide YY, as well as a large number of inflammatory markers.[65] These predictors may be classified into two broad groups based on their mechanism of action. The first group includes indices for preserved pancreatic beta-cell function, including younger age, shorter duration of diabetes, and lack of insulin dependency. The second group tracks insulin resistance, including baseline BMI and amount

of visceral fat. Several validated prediction models for diabetes remission have been produced to help guide clinicians. However, the precise utility of these models still needs further verification in prospective, randomized controlled studies and long-term follow-up.[66] So, whilst bariatric surgery has been shown unequivocally to reverse T2DM and to be of great benefit in obese patients, further studies are under way to pinpoint more effective patient selection and post-operative follow-up to mitigate the risk of complications and increase or optimize the levels of long-term benefit and remission.

Taylor Twin Cycle Theory

Blood glucose levels return to normal within a week of bariatric surgery. Initially, it was postulated that bariatric surgery produces this early normoglycemia via a direct effect on incretin hormones. However, incretin hormones are secondary regulatory hormones, and are less likely to be the driver of an almost immediate change in fasting plasma glucose. A careful review of the data from Guidone et al[67] begins to shed more light on what could be happening in the body after bariatric surgery. In patients who elect to undergo bariatric surgery, there is an obvious and stark change in calorific intake following the procedure. The immediate consequence is negative calorie balance, and the body has to use its energy reserves. Instead of an abundance of post-prandial fatty acid intermediates (that inhibit glucose metabolism) being left to accumulate in the cytoplasm,[68] they are urgently taken up by the mitochondria for oxidation. Diacylglycerol, the product of removing one of the three fatty acids from triacylglycerol (ie, triglyceride), rapidly decreases in concentration and suddenly cells are left with a normal choice of fuel—either glucose or fat, depending upon needs. This postulated sequence of events has been drawn together as the Taylor Twin Cycle Hypothesis,[69] which is a considered attempt to explain why T2DM could be reversible.[70]

According to the Taylor Twin Cycle Hypothesis, during chronic over-consumption of energy-dense sugary foods, the excess carbohydrate is removed by lipogenesis, and this particularly promotes fat accumulation in the liver. As insulin promotes this lipogenesis, individuals with a predisposition for, or a pre-existing degree of insulin resistance (determined by genetics or lifestyle factors) will accumulate liver fat more easily than others because of the higher plasma insulin levels. Fat deposition in the liver, trackable by rising serum ALT levels, will cause resistance to insulin suppression of hepatic glucose production. If left unchecked over many years, the resulting hyperinsulinemia will accelerate the conversion of excess calories into liver fat. This creates a vicious cycle of insulin resistance, hyperinsulinemia, and fat deposition in the liver.[71] To deal with the fat, a fatty liver increases its export of VLDL triacylglycerol,[72] which adds to the problem of elevated levels of free fatty acids in the blood from any unhealthy diet. This fat can be taken up by B islets in the pancreas. Eventually, the twin process of fatty acid uptake in the islet cells and insulin resistance will reach a threshold level, causing B cell dysfunction, and precipitating impaired glycemic control followed by frank T2DM.[73] After bariatric surgery, this whole mechanism could be thrown into reverse because of the stark change in calorie balance. The excess toxic fat in the pancreas is quickly eliminated, and B cell function appears to be re-established. A recent study has suggested that as little as 0.5g of excess fat can cause severe dysfunction in the pancreas. A mere 0.5g can quickly be eliminated, possibly explaining why normoglycemia is established so astonishingly quickly – with the caveat that such a small amount is also very easy to re-accumulate. So, whilst reversal might be very quick, maintaining reversal for longer periods (ie, long-term remission), will require a further period of dietary restriction.[74] The Taylor Twin Cycle Theory will allow scientists to study further how medical interventions might be designed to have similar beneficial effects to bariatric surgery without the need for the invasive anatomic rearrangement. Figure 2 depicts the main processes of the Twin Cycle Theory and how they could combine to effect T2DM remission.[69]

Pharmacotherapy for T2DM- from Reversal to Remission

Most T2DM guidelines have focused on the pharmacological management of hyperglycemia, rather than weight loss, which was always a part of core management.[75] The increasing use of hyperphagic drugs like insulin and sulphonylureas was a further contradiction.

It is a sensible view that pharmacotherapy alone cannot address underlying unhealthy lifestyles leading to overweight. Overweight/obesity is strongly driven by genetic factors that makes it a chronic problem with a high risk of relapse. Compounding this state of affairs is an obesogenic environment within which sugar and the pleasure of eating can be

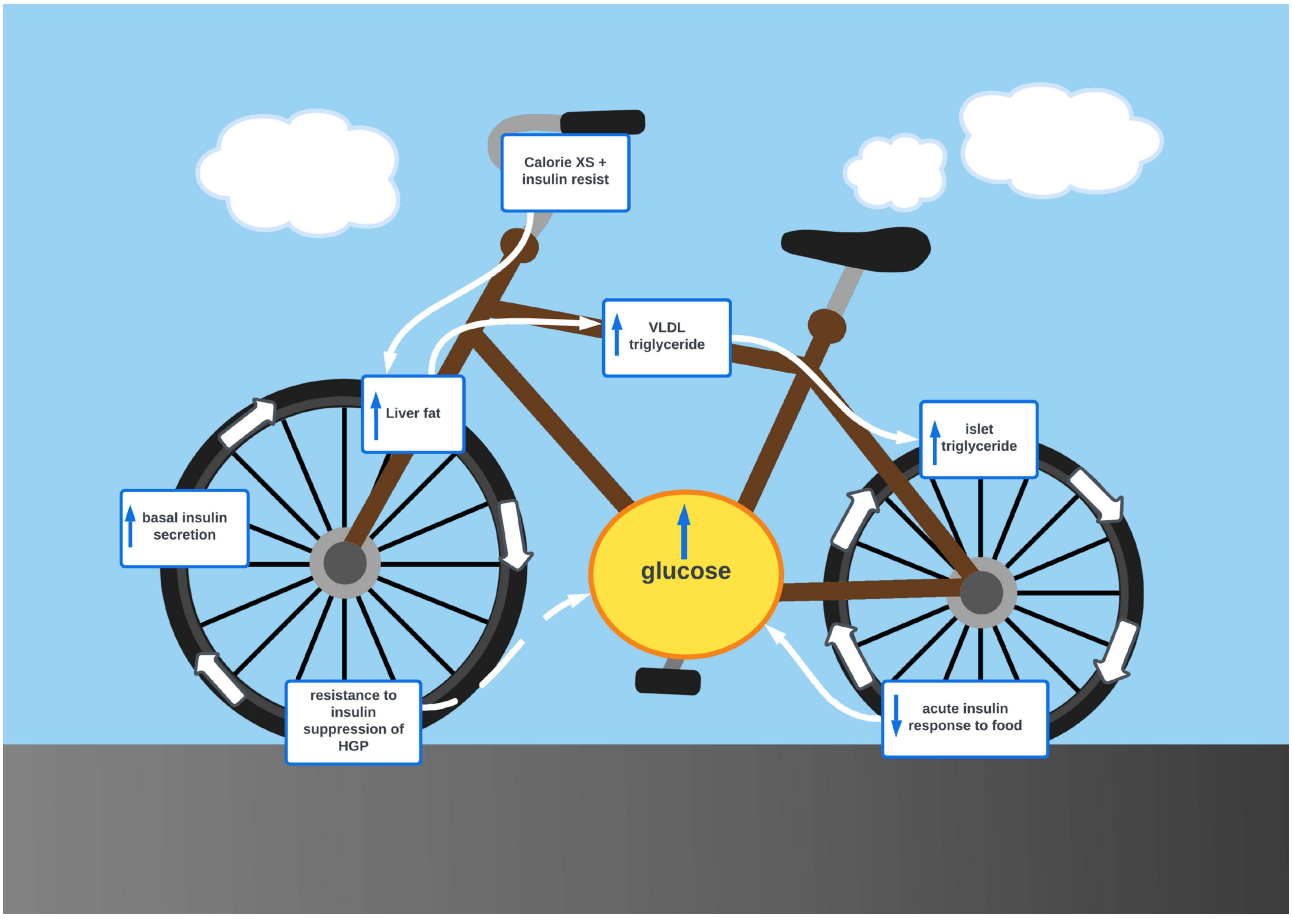

Figure 2 The Taylor twin cycle theory.
Notes: This bicycle is controlled by handlebars representing chronic, excess (XS) calorie intake in the presence of muscle insulin resistance. Raised plasma insulin levels will expedite chronic excess calorie storage from carbohydrate via de novo lipogenesis, and hence promote liver fat storage. This will cause the liver to become relatively resistant to insulin and a small increase in plasma glucose will occur. In turn, insulin secretion will increase to reduce plasma glucose. The further increased insulin levels will bring about a self-reinforcing cycle. Excess fat will result in increased export of VLDL triglyceride from the liver, uptake by islets and inhibition of meal insulin secretion. At a personal threshold, the level of pancreatic fat imposes too great a load and plasma glucose levels will then rise relatively rapidly.[69] Adapted from Taylor R. Banting Memorial lecture 2012: reversing the twin cycles of T2DM. *Diabet Med*. 2013;30(3):267–275. © 2012 The Author. Diabetic Medicine © 2012 Diabetes UK.
Abbreviation: HPG, hepatic glucose production.

addictive. Even if medication could solve lifestyle disease on its own, the prospect of medicating the majority of the population is not one that can be entertained without considering all the side effects and cost.[76] A recent analysis reported that between 2011 and 2017, additional benefits from the diabetes drugs approved by regulators were found in only 16% of patients.[77] If conventional glucose-lowering pharmacotherapy is used without considering an individual strategy for reversal, T2DM is usually a progressive disease.[10] This disappointing state of affairs is at least partly because conventional pharmacotherapy has been developed to treat the levels of blood glucose, whilst the underlying etiology of T2DM is, in reality, much more complex, and for example, associated with visceral fat.[78,79] It is a sobering fact that increased US expenditure on conventional diabetes care has not improved outcomes.[80] Perhaps, the most depressing data come from a major study by Kaiser Permanente that found only a 0.23% remission rate with best practice standard care.[81]

However, revisiting the literature around pharmacotherapy for T2DM more carefully reveals that these otherwise depressing trends even with "best practice" were not left unchecked by pioneering researchers who prioritized exploring interventions that could be effective for remission.

In fact, the feasibility of reversing T2DM with pharmacotherapy has been demonstrated in numerous studies and with different medications – therapeutic strategies that have not been adopted as first-line. Studies have shown that, when

implemented early in the course of T2DM (ideally less than 2 years), intensive insulin therapy for 2–3 weeks can induce a glycemic remission, wherein patients are able to maintain normoglycaemia without any anti-diabetic medication. When followed-up in a meta-analysis, short-term intensive insulin therapy was found to significantly improve islet function and induce remission in 46% of patients at 12 months, and 42% at 24 months. This effect is not weight-loss dependent, and patients were not administered with VLEDs or LCDs. Beta-cell redifferentiation was considered the important underlying mechanism for the treatment effect. Short-term intensive insulin therapy can improve the underlying pathophysiology in early T2DM, and this approach clearly provides one treatment strategy for modifying the natural history of the disease.[82–87]

Jennings et al found a triple therapy of metformin, pioglitazone and repaglinide to be effective for reversing newly diagnosed T2DM patients. The drugs were given at maximum tolerated doses and then tapered according to results.[88]

Panikar et al found a multidrug therapy consisting of metformin, pioglitazone, and gliclazide effective for reversal in a population of T2DM patients of less than 24 months duration.[89]

Even for T2DM patients who have had the disease for 5 years and progressed to insulin (but before the advent of any serious co-morbidities), add-on drug therapy with metformin, glibenclamide, and pioglitazone saw 43% lose their requirement for insulin altogether at 6 months.[90]

Elsewhere, there is the anti-obesity drug orlistat, which has been available for over 2 decades. It is a peripheral lipase inhibitor which has virtually no systemic absorption and an excellent safety profile, despite initial (unfounded) fears about liver injury.[91] Orlistat could be considered a calorie restriction mimetic (CRM), a type of drug that otherwise mimics the mechanism of action, effects, and long-term outcome noted with calorie restriction, without actually causing calorie restriction or lack of food intake.[92] Interventions that can mimic energy deficit can drive similar beneficial effects on T2DM as bariatric surgery.

Orlistat is often overlooked by practitioners because of its gastrointestinal side effects (oily stools, soiling), causing poor patient compliance. However, gastrointestinal side effects can be greatly mitigated by careful patient selection, giving clear instructions to patients on how to follow a low-fat diet, and starting with a lower dose (60mg capsule instead of 120mg). The horror stories about oily stool are associated with starting on the higher dose (120mg) and poorly informed patients who use the orlistat inadvertently when on an ad libitum diet or with fried food, despite dietary advice.

If prescribed with due care and patients can tolerate the drug, then the improvements in glycemic profile seen in orlistat-treated diabetic patients[93,94] are comparable to those on antidiabetic medications[95–97] Orlistat also improves glycemic control and reduces insulin requirements when it is added to insulin monotherapy in T2 diabetes.[98] Similar results were found in those treated with oral hypoglycemics.[99–101] In one of the largest studies of its kind on diabetes prevention, orlistat was found to prevent and delay pre-diabetes from progressing to frank T2 diabetes.[102]

The improvements with orlistat can be seen both in the long and short term. In the long term, orlistat improves glycemic control by effecting accelerated weight loss[103] even with diabetic patients, a group who are known to have particular difficulty losing weight when compared to non-diabetics.[104] In addition, orlistat improves glycemic control more than would be predicted by equivalent weight loss through diet and exercise programs.[98,105–107] And interestingly, if we look more closely at the literature, in the short term we see that many studies have even reported that improvements in glycemic control and insulin sensitivity are seen very shortly after orlistat is started, before any weight loss has occurred.[108,109] These observations tie in with the results of other research on T2DM and body fat. If we look at weight distribution in T2DM patients, they are more likely than non-diabetics to have an increased abdominal circumference. Increased intra-abdominal adiposity is often a surrogate for visceral fat deposition around the liver and pancreas, which in turn is closely associated with T2DM risk.[110,111] Visceral fat is a source of several pro-inflammatory cytokines that increase insulin resistance[112] and reduce the survival of pancreatic B cells.[113] Orlistat selectively reduces visceral fat rather than other body fat stores, and therefore attenuates the harmful cytokine production, whilst boosting adiponectin.[93,114–119] It has long been known that free fatty acids increase peripheral and hepatic insulin resistance, inhibiting whole body glucose utilization and oxidation, thereby increasing hepatic glucose output, and affecting virtually all major pathways involved in glucose metabolism.[120–127] HbA1c levels are also positively associated with total fat intake.[128] Orlistat blocks the digestion (and therefore absorption) of free fatty acids from the diet. Patients treated with orlistat recover much greater insulin sensitivity than patients who are given behavioral interventions plus placebo, even when the reduction in hepatic steatosis, loss of skeletal muscle fat content, changes in visceral fat tissue, and

amount and rate of weight loss remain unchanged.[106] Improvements in insulin sensitivity are therefore not modulated by weight loss alone, and plasma free fatty acid levels could in fact be a much stronger and more immediate correlate of insulin sensitivity both at baseline and after weight loss. In obese individuals, levels of free fatty acids are elevated, especially after unhealthy meals, and this is associated with their state of increased insulin resistance.[129,130] Reduction in the levels of free fatty acids in obese individuals with pre-diabetes or diabetes improves their glycemic control.[124] Not surprisingly, obese type 2 diabetics have consistently shown improvements in glycemic control with orlistat use.[93,101,118,119] Orlistat has positive effects on gut peptide hormones, resulting in an incretin-like response. The increase in the passage of intestinal fat content due to orlistat blockade stimulates increased secretion of two gut hormones, GLP-1 and GIP,[131] which in turn boost insulin secretion.[132,133] GLP-1 secretion is also associated with accelerated weight loss.[134]

In practice, orlistat is often overlooked by clinicians due to its socially embarrassing side effects. However, given its proven benefits, more effort should be made to overcome this barrier. Greater attention when giving appropriate low fat dietary advice, and perhaps considering starting on lower dose (60mg) of orlistat, would greatly mitigate any embarrassing side effects. Making the drug more socially acceptable by removing the greatest barrier to its more widespread use would greatly benefit T2DM patients. Interestingly, studies of orlistat with a modified-release version of alpha-glucosidase inhibitor acarbose showed much improved tolerability of orlistat. Data on weight loss outcomes with the combination are still awaited.[135,136]

Kalra et al[92] elaborate on glucose-lowering drugs that are CRMs. Of the various anti-diabetic medications, four classes are identified: insulin sensitizers (pioglitazone, metformin), the alpha-glucosidase inhibitors, GLP-1 agonists, and SGLT2 inhibitors, as summarized in Table 2.

A study in Japanese patients found the alpha-glucosidase inhibitors effective for reversal in obese type 2 diabetics, with miglitol most effective (followed by voglibose, whilst acarbose did not accrue benefits in the study timeframe of 12 weeks). Interestingly, the vast majority of patients in this study were on a number of concomitant medications, and the beneficial effects likely resulted from the inadvertent multi-drug therapy administered by the authors, aided by the CRM. The authors postulated that acarbose required more than 12 weeks use to accrue reversal benefits. The authors did not mention how long the patients had had T2DM.[137]

Since 2021, it has been seen from Phase 3 trials that high dose GLP-1 analogues (like semaglutide) or GLP-1/GIP dual analogues (like tirzepatide) can deliver stunning results and promise to be game-changers in the realm of T2DM reversal. In the SURPASS-1 study of tirzepatide, treatment differences for two estimands – efficacy and treatment-regimens – were evaluated for the three tirzepatide doses (5 mg, 10 mg and 15 mg) compared to placebo for 40 weeks. Astonishingly, 51.7% of participants assigned the highest dose (Eli Lilly; 15mg) achieved an HbA1c of 5.7%, which is considered a nondiabetic level. Average weight loss was 9.5 kg (11.0%) at 40 weeks. Participants had a mean diabetes duration of 4.7 years and baseline HbA1c and weight of 7.9% and 85.9kg respectively. There were no events of severe hypoglycemia or severe hyperglycemia in the tirzepatide treatment arms. The most commonly reported adverse events were gastrointestinal-related and these were mild to moderate in severity, usually occurring during the dose-escalation period. Treatment discontinuation rates due to adverse events were less than 7% in each tirzepatide treatment arm.[138] Tirzepatide has been shown to be as effective for type 2 diabetics on insulin with up to 62.4% of treated participants using the highest dose (Eli Lilly; 15mg) achieving an HbA1c level of less than 5.7% at 40 weeks.[139] In a 68-week study of semaglutide in type 2 diabetes, subjects on a high dose of the drug (Novo Nordisk; 2.4 mg) lost an average 9.6% of

Table 2 Examples of Glucose-Lowering CRM Drugs

Biguanides: metformin
Thiazolidinediones: pioglitazone
Alpha-glucosidase inhibitors: miglitol, voglibose, acarbose
GLP-1 receptor agonists: semaglutide, tirzepatide
SGLT2 inhibitors: empagliflozin (and others)

their body weight, compared with an average weight loss of 7% on 1mg of the drug, and 3.4% with the placebo. At the higher dose, more than a quarter of the participants lost over 15% of their weight, almost half lost 10%, and two-thirds lost at least 5%. The average reduction in body weight with high dose semaglutide was 10kg. These results have been hailed as among the best ever seen with any weight loss medication in patients with T2DM. At the end of the trial, participants on the high dose had an average HbA1c of 6.4%, which is just in the prediabetes range, and therefore below the threshold to diagnose T2DM. This compared with 6.6% on a 1 mg dose (still diabetic) and 7.8% on placebo. The most commonly reported side effects with high dose semaglutide were gastrointestinal issues including nausea, vomiting, diarrhea, and constipation, which 88% of participants reported.[140]

It should be cautioned that there are no data yet to see if reversal mediated by GLP-1/GIP analogue drugs can be maintained long term without dependency on the drugs. Under the strict ADA definition of remission, reversal of T2DM dependent on continued use of GLP-1/GIP analogue drugs might not be regarded as remission if the drugs are considered to be glucose-lowering drugs rather than weight loss agents.

Dutta et al[141] point out that when it comes to using pharmacotherapy for weight loss, especially in type 2 diabetics who are more brittle slimmers, combination therapy rather than monotherapy will be the only feasible strategy to achieve the required weight reduction required for reversal and remission. The kind of weight loss required for successful reversal and remission, as has been keenly observed by Dutta et al, is much more likely with combination pharmacotherapy.

The observations of Dutta et al[141] about the need for multi-drug therapy is supported by almost all studies of combination pharmacotherapy for weight loss, wherever data is available, especially in the context of T2DM reversal and remission, albeit at a cost of a theoretically increased risk of side effects. Unfortunately, studies with comprehensive data on all the permutations of multi-drug therapy for weight loss and reversal in T2DM are scant – for example, there are no data on the combination of orlistat with the other alpha-glucosidase inhibitors like miglitol or voglibose, themselves on their own, or in combination;[137] and very little data on orlistat with GLP-1 agonists or orlistat with SGLT2 inhibitors- to name a few gaps in the literature.[141,142]

Notwithstanding, new studies (even if anecdotal or case reports) are being published all the time about multi-drug combinations – for example, Chua's paper on high dose liraglutide (a type of GLP-1 agonist) and SGLT2 inhibitor.[143] With each new publication, we have a slightly clearer picture of which combinations of drugs can be used, and in which circumstances.

Very Low Energy Diets (VLEDs)

When it comes to the nutrition therapy of T2DM, standard practice has been kept in alignment with generic public health advice and health promotion targets, without specifically aiming to achieve remission. Nutritional management of T2DM is focused on improving glycemic control through moderate weight loss.[75,144] Moderate weight loss (ie, 5% body weight) improves glycaemic control significantly, but is usually not sufficient to achieve remission. A retrospective cohort study of T2DM patients receiving standard ADA care (including dietary advice) found a 7-year cumulative remission rate of just 0.14%.[81]

Born out of this depressing state of affairs, researchers have been exploring different approaches to the nutritional management of T2DM for a long time. Early, dramatic improvements in fasting plasma glucose, prior to significant weight loss, have been observed with VLEDs long ago in the overweight or obese T2DM patient, even in the absence of any pharmacotherapy.[145] Although achieving normoglycemia was easy, maintaining it as a durable remission required sustained weight loss in overweight type 2 diabetes. And it should be noted that some 90% of adults in the UK with T2DM are overweight or obese.[146] In 1976, Bistrian et al reported a small study with seven T2DM patients with obesity on insulin demonstrating that a very low energy diet rapidly eliminated the need for insulin in all participants. This was achieved in an average of just 6.5 days, with the longest taking 19 days.[147] Bauman et al showed that a low energy diet led to significant improvements in glycemic control.[148] Another study showed that low energy dieting and gastric bypass in type 2 diabetes could be equally effective in improving glycemic profile in the short term.[149] However, the diet group only maintained weight loss for the first 3 months on average, confirming the difficulty of long-term maintenance using dietary approaches, reported in many other studies.[23,150–153]

For individuals with diabetes, the Look AHEAD (Action for Health in Diabetes) study showed that a loss of 5–10% of body weight could improve fitness, reduce HbA1c levels, improve cardiovascular disease (CVD) risk factors, and decrease use of diabetes, hypertension, and lipid-lowering medications,[154] however the idea that weight loss as a potential approach for long-term remission was not considered at the time. The conventional wisdom was not seriously questioned until the seminal DiRECT study, which demonstrated that T2DM can be successfully reversed for the long term with a very low energy diet. In fact, 50% of the participants had long-term reversal with a weight loss of 10kg, and 90% with 15kg provided that this was achieved within 6 years of their diagnosis. After 6 years, or if already on insulin, T2DM was still potentially reversible, but remission was more difficult, took longer, and was more fragile.[155] On average, the participants in DiRECT had achieved 10–15kg of weight loss, translating to remission for 46% of their patients at 1 year, and 36% at 2 years follow-up.[156] The DiRECT trial used a structured approach with evidence-based (entirely non-surgical non-pharmaceutical) behavior change interventions to deliver the initial weight loss, a result all the more worthy of admiration as all treatment was delivered via routine care in general practice. This was despite the fact that GP clinics are given few resources to attend to challenging areas of practice such as weight management. In a further study, the number of participants has been expanded to 5000 and follow-up extended for a further 3 years, to assess the long-term outcome of diet-induced weight loss on remission.[157] The DiRECT authors surmised that remission (or significant improvement in glycemic control) would be maintained long term by careful weight maintenance or perhaps further weight loss at a later stage.[158] The DiRECT approach and impressive results (61% remission rate at 12 months) were replicated in the DIADEM-1 study in Qatar, in a totally different Middle Eastern and North African population, showing that the DiRECT approach could work equally well outside of a UK population.[296]

Researchers have analysed the profiles of those patients who were able to achieve remission. Those who had positive outcomes were male, younger, with good mental health, on fewer medications, had shorter duration of T2DM (less than 6 years and ideally less than 2 years), higher fasting insulin, and lower fasting glucose at baseline. Importantly, they had less pancreatic and total body fat, although there was no difference in hepatic triglyceride content. Interestingly, the key feature distinguishing responders from non-responders was the return of the first-phase insulin response. Responders showed an improvement in first-phase insulin response, whereas non-responders showed little or no change. Combining these data, there seems to be a point at which B-cell function declines to such a degree that it cannot recover from lifestyle interventions alone, even though those interventions can still induce significant clinical improvements.[159,160]

The Role of Counselling and Behavior Change

The American Heart Association (AHA) recommends the implementation of behavior change techniques for promoting lifestyle change.[161]

A study published in the Journal of Human Nutrition found that weight regain (after initial rapid weight loss) can be significantly slowed down, but not eliminated, once a normal diet is restarted, if there is structured psychological support using cognitive behavior therapy.[162] Over the past 3 years, a frenzy of health-care start-ups have launched digital (online) solutions and apps focused on delivering weight loss through digital behavior change techniques, and it is interesting to note that these psychological approaches do indeed deliver modest results for weight loss much more than would be expected from an entirely non-surgical and non-pharmaceutical intervention. Perhaps, the most thorough evidence-based digital behavior change program of its kind is that of Changing Health based on the Southampton POWeR (Positive Online Weight Reduction) study, which has partnered with the NHS in the UK.[163] The evidence from the POWeR study suggests that this approach – digital written content with occasional brief nurse follow-up – could be a very scalable model that improves outcomes from dietary approaches to weight loss, and by extension, should contribute to better outcomes if combined with all approaches to T2DM reversal.[164,165]

Further research needs to be done on the extension of digital behavior change outside of dietary approaches to reversal, but the results are already highly anticipated. For example, Novo Nordisk has already partnered with Noom to deliver behavior change to those using its ground breaking GLP-1 pharmacotherapy.[166]

There is also a lack of studies directly comparing delivery methods for counselling (eg, individual vs group-based, face-to-face vs online) with a counsellor. Some studies have used intensive lifestyle interventions whilst others have had

the minimum of contact time. The online methods allow an increase in intensity of the intervention using automated reminders and intelligent-driven personalized content with only minimal contact time. Interestingly, simply increasing contact time with a counsellor did not improve outcomes.[167,168]

In vitro Studies and Remission of T2DM After VLED's

In vitro studies have provided parallel evidence that remission from T2DM really is possible at a cellular level. A study published in Cell Metabolism showed that the B-cells of the pancreas can indeed recover their ability to synthesize insulin after remission through weight loss.[169] The restoration of B-cell function and the resumption of exports of very low-density lipoprotein from the liver were salient features of the cellular remission seen.[169–173]

All of this adds to the feasibility and validity of VLEDs for reversing T2DM. For T2DM patients who are of normal weight or are underweight, it is still thought that weight loss can bring about remission, albeit by a much smaller amount. The DiRECT authors are already studying this group and more data will be available soon.[174] As noted by others, Newcastle University found that it was as little 0.5g of excess toxic fat in the pancreas that was causing insulin production failure in B-cells, which might explain how those of normal weight could still have the problem.[74,175]

Despite the optimism generated by the DiRECT trial results, a feature of studies of all VLEDs not to be forgotten is that remission is not universal. Less than 40% of participants have good long-term outcomes. VLEDs can only be prescribed for 12 weeks by practitioners, and the main challenge now is to improve long-term remission rates after initial reversal using this dietary approach. Weight maintenance interventions have yet to definitively tackle all the issues around appetite resurgence once a normal diet is reintroduced. A major criticism of VLEDs (like the one used in the DiRECT trial) is that they do not rely on meals made from natural whole foods, but instead opt for processed, total diet replacement drinks[176] and this also could put patients at risk of micronutrient deficiencies, requiring preventive supplementation with multi-vitamins.[177]

Low Carbohydrate Diets (LCDs)

There are several different definitions of a low carbohydrate diet (LCD) based broadly on restricting carbohydrate intake to anywhere between 20g–130g of carbohydrates per day (equating to 6–26% of total energy intake).[178] The Scottish Intercollegiate Guidelines Network (SIGN) suggests that "a minimum of 50g of carbohydrates per day appears safe for up to six months" for type 2 diabetics.[179] The classification of LCDs by Feinman et al[180] has become the most popular definition among dietetic practitioners, as summarized in Table 3.

Before the discovery of insulin in 1921, LCDs were the default dietetic approach to diabetes.[181,182] In fact, LCDs are not new and have been promoted for cardiovascular health since at least the time of William Banting in 1863.[183] However, the advent of injectable insulin and oral hypoglycemics led to a paradigm shift in the dietetic management of T2DM. Around the world, drug companies drove the strategy of relatively higher carbohydrate, lower fat diets, with the aim of controlling sugars with the use of their medications – not a surprising strategy, assuming the principal aim of drug companies is to promote strategies that sell their medications.[184,185] In the 1980s, public health advice in the UK was pushing the "low fat" and "low cholesterol" message, whilst staying silent on the consumption of refined carbohydrates,[186] facilitating the trend of increased consumption of low fat, high carbohydrate processed foods. In fact, between 1961 and 2011, the same trend was seen in the USA where 90% of the increase in calorie intake came from

Table 3 Definition of LCDs After Feinman et al[182]

Definition	Carbohydrate (g/Day)	Carbohydrate (% of Energy)
Very Low Carbohydrate Diet	20–50g	6%-10%
Low Carbohydrate Diet	<130g	<26%
Moderate Carbohydrate Diet	130g-225g	26%-45%
High Carbohydrate Diet	>225g	>45%

carbohydrates and polyunsaturated vegetable oils.[187] The meteoric rise in diabesity over the past decade in the UK and USA, following an increase in the consumption of refined carbohydrates, makes it unlikely that it was entirely coincidental, but more likely that the increased consumption of refined carbohydrates was one of the aggravating causes of the diabesity problem that we face today. It is paradoxical that the poorly educated Queen Marie Antoinette of France has been vilified for generations for allegedly proposing to let the masses "eat cake" to satisfy their hunger- an attribution that most historians now think was part of revolutionary propaganda and not actually factual;[188] yet this seems very similar to what policy makers in the West were happy to recommended to the public for several decades, whilst food manufacturers took advantage of the liberal regulations to flood the marketplace with processed, calorie-dense foods using highly refined sugars. Today, the recommended NHS guidelines in the UK allow the daily consumption of 30g of "free sugars" (added sugars plus naturally-occurring sugars in certain foods) as being within normal limits for normal adults, equating to no more than 5% of total energy intake. However, this UK government recommendation does not include the sugars found naturally in milk, fruit or vegetables, which are included in total carbohydrate counts elsewhere.[189] Public health advice about carbohydrate consumption is changing. A report by the Scientific Advisory Committee on Nutrition in May 2021 sets out a body of evidence that low carbohydrate diets have a role to play in T2DM management and reversal, a role that requires further study in order to be optimized and individualized.[190]

The "high carbohydrate low fat" approach of previous decades was challenged with the popular re-discovery of LCDs by Dr Atkins in 1972.[191] Sceptics of the conventional approach to carbohydrates like Dr Atkins pointed out that there was no evidence of a dietary or biological requirement for so much sugar in the human diet. Added sugar had no obvious nutritional value. Dietary fructose or sucrose were not known to be an essential part of any biochemical process in the human body. No studies have demonstrated the health benefit of consuming sugar.[192] Today, some authors question whether consuming carbohydrate (excluding fibre) is essential for human function at all.[193] The scientific ambivalence about dietary sugar has been growing, especially over the past decade.[194] Excessive refined and starchy carbohydrates have been found to increase the risk of developing poorly controlled blood glucose levels, and therefore the chances of progressing to T2DM and its morbid complications, and these food choices could increase the risks independent of calories or weight gain.[195–197] The underlying mechanisms for the harm caused by unhealthy carbohydrates are no longer obscure. For example, it has been found that the plasma level of the saturated fat palmitic acid, linked to the consumption of starch, sugar, and alcohol, is strongly associated with T2DM.[198,199] The same calories from different foods can have very different metabolic impacts on the body, and it has been suggested that, after digestion and absorption, some foods are metabolized in such a way that they may promote metabolic disease, an effect that is over and above merely measuring the impact of their calorific content. Isocaloric portions of sugar, alcohol, meat or olive oil have very different effects on thermogenesis, insulin resistance, appetite regulation, and the gut microbiome – a situation which becomes even more complex when we add the interaction with an individual's genetics.[200] It appears that calories are not the only variable to consider, even though recent messaging from some clinical academics has been focused on the point that "diabetes is caused by chronic calorie excess",[157] whilst remaining silent on the additional deleterious role of carbohydrates within that excess of calories. A recent review in the BMJ explicitly discussed the importance of the quality of carbohydrates and their links to developing a multitude of chronic diseases. Whilst the consumption of refined sugars has been linked to the etiology of chronic disease, on the other hand, highly viscous plant fibres which, paradoxically, are also carbohydrates, are the diametric opposite, helping to reverse type 2 diabesity and reducing the risk of morbid cardiovascular complications. This reinforces the concept of high-quality versus low-quality carbohydrates, based on their glycemic index and glycemic load, which are the two key empirical metrics to rank foods according to their effects on blood glucose.[201]

At the same time, much evidence has been published on restricting carbohydrate intake–not just sugars, but also grains and starchy vegetables–and has found that T2DM can improve dramatically or disappears with this approach.[168,202–235] One review concluded that restricting dietary carbohydrates was the "single most effective intervention for reducing all the features of metabolic syndrome" and should therefore be the first approach in diabetes management. The greatest reductions in HbA1c and diabetic medication use were seen when carbohydrates were restricted to <10% of calorie intake.[236] The evidence includes a number of short-term studies, including a meta-analysis, all of which found that low carbohydrate diets are highly therapeutic for diabetes.[42,168,203,207,213,218,223,236–238] The improvements in glycemic control usually appear early

and before significant weight loss.[224] An advantage is seen in glycemic control in trials where a low-carbohydrate group is compared to a control group for a given weight loss.[168,217,233] Another interesting feature of low carbohydrate diets is that, even if prescribed ad libitum to the participants with no obligation to restrict calorie intake in the study protocol, a spontaneous calorie restriction is quite often seen,[239,240] perhaps suggesting that intake of unhealthy carbohydrates is associated with increased appetite. Evidence from short-term studies suggests that low carbohydrate diets produce greater (or at least the same) weight loss as traditional low fat (and low calorie) diets.[240–250] 2-year results from a recent ad libitum low-carbohydrate T2DM trial, which included patients with a longer duration of diabetes (8.4 years on average) and which did not exclude any patients on insulin, were very surprising. Normoglycaemia (off medications other than metformin) was achieved in 54% of those completing the study, and 74% were able to maintain the diet and complete the study, suggesting retention was higher than with normal diets. Typically, weight loss of 10% was recorded despite no calorie restriction.[232]

Adding to the general cause of LCDs, few of the studies have accounted for the withdrawal of drugs much more rapidly in the carbohydrate restriction arms than in control arms, perhaps underestimating the benefits of LCDs in some instances.

Dr David Unwin, an innovative GP expert in diabetes, has published evidence of the cost-benefits of low carbohydrate diet promotion in general practice, demonstrating significant savings from curtailed prescriptions. If all 9400 GPs in the UK chose to replicate Dr Unwin's approach, the immediate savings could reach £423m annually for the NHS. This does not take into account the long-term savings in human and financial terms of preventing morbid complications of diabetes like blindness, strokes, peripheral arterial disease, renal failure, and heart attacks.[156,251] It should be noted that attention from a long-time primary care practitioner might induce a motivating factor for patients out of loyalty and attachment that skews the data about LCDs from primary care practitioners- the so-called "practitioner effect".

Low carbohydrate diets may also have an advantage for long-term weight maintenance. A variety of powerful epigenetic and genetic factors will drive weight regain after all types of successful weight loss program, usually as a result of a surge in appetite. Interestingly, participants assigned to a low carbohydrate diet after losing weight had significantly higher energy expenditure and lower levels of ghrelin (higher levels of which are presumed to lower energy expenditure and increase rebound appetite) than those assigned to a high carbohydrate diet. Total energy expenditure after weight loss was increased in those assigned a low carbohydrate diet with a linear trend of 52kcal per day (95% CI 23 to 82) for every 10% decrease in the calorific contribution of carbohydrate to total energy intake during weight maintenance.[252]

Low carbohydrate diets have been endorsed as an appropriate diet pattern by the ADA and the European Association for the Study of Diabetes (EASD).[253,254] The WHO has published the LIMIT recommendations on dietary carbohydrates,[255] and the introduction of sugar taxes in the UK (and elsewhere) could be followed by further policy measures if the results are positive.[256]

It is not known if restricting carbohydrates is easier for some patients than others, compared to reducing calories in general. Carbohydrates are addictive and quitting unhealthy sugars may be as difficult as smoking cessation.[257] Dr Michael Mosley, another GP expert in low carbohydrate slimming, clearly alludes to the challenges of carbohydrate restriction for some patients in his articles, although he does not try to quantify or measure this aspect.[258]

A major limitation of the LCD literature base is that there are few studies of LCDs showing T2DM remission without also reporting weight loss. It is difficult to attribute pure causality to the LCD as a result. The underlying T2DM pathophysiology may still be intact, although not being fueled, unless there is weight loss. As soon as normal dietary patterns return, so could the T2DM. The other limitation of LCD literature is the lack of long-term studies, partly because it might be difficult to maintain a pure LCD for the long term. However, in practical terms, if the patient is able to maintain carbohydrate restriction appropriate for their personal threshold for euglycemia, it makes little difference to their continued enjoyment of euglycemia.

A major complication of the story of LCDs is that some advocates of these diets have advanced very controversial versions, in particular those which include a high fat intake,[259] causing debate and paradoxically probably slowing down their more widespread adoption by health-care practitioners.[260] It should be the common sense position that there is no one-size-fits-all prescriptive approach to making food choices, including restricting carbohydrates. Food choices should

be underpinned by scientific evidence with the aim of achieving treatment goals, improving health, and quality of life. To improve compliance, they should also be acceptable and enjoyable. An individualized approach will need to be taken to some degree when practitioners want to advise on restricting unhealthy carbohydrates. Whilst the tolerance threshold for consumption of refined and starchy carbohydrates in patients with pre-diabetes and T2DM is a personal threshold, it is still likely to be much less than the average in normal individuals. In any single individual patient, the personal tolerance level for unhealthy carbohydrate intake will to some degree be moderated by other factors like exercise and genetics. More longer-term studies of LCDs with standardized definitions and comparable methodology will be required to determine and classify the optimum approach in patients and to maximize the duration of the associated metabolic benefits. Studies are still required to elucidate any long-term side effects and how to mitigate them.

Which Diet is Superior?

The published papers and real-world examples for both VLEDs and LCDs vary tremendously with respect to quality, robustness, numbers enrolled, counselling intervention strategy, intensity, and length of follow-up. With no direct, high-quality comparison of VLEDs and LCDs, it is not possible to say which is superior for T2DM remission. Like for pharmacotherapy, it would not be surprising if some combination of both approaches might be best of all. There is no evidence to suggest that it is not feasible to combine the approaches.

Even if a study were designed to compare VLEDs and LCDs, like all dietary research, it would not be realistic to expect participants to adhere purely to any dietary recommendation over a long period, effectively meaning that dietary trials are not randomized. This is apart from the fact that it is difficult to control carbohydrates as sugars are addictive.

It should also be remembered that not everybody with T2DM is overweight or obese. More research is needed to elucidate what dietary approach is most appropriate for this group. It might be that LCDs are more appropriate in patients who are normal weight as calorie restriction would not be required.

Exercise

For over 10 years, there has been a general consensus that exercise improves glycemic control.[261,262] However, many people with diabesity are unable or unwilling to take exercise. Obesity alone can discourage exercise, for example if there are concomitant joint problems.[263–266] Many diabetic patients who could take exercise, still choose not to, for many reasons, and until now, no behavioral interventions have been successful in reversing this problem.[267] Therefore, prescribing sudden exercise on its own is less likely to be an effective first-line treatment to achieve remission of T2DM. There is little evidence that there is sufficient compliance with prescription exercise by T2DM patients to make a significant impact on diabetes in the population. However, thoughtfully structured exercise as an add-on, when prescribed carefully and in consideration of the context of the patient's behavioral/psychological, musculoskeletal and cardiovascular status, can only accelerate and improve outcomes when combined with other approaches. As a minimum, practitioners should remember to advise the maintenance of usual physical activity, whilst avoiding any sudden surges, during dietary interventions for weight loss.[268]

Where it is possible to prescribe it (and some compliance is forthcoming), the impact of exercise in T2DM reversal might be maximized in the maintenance phase when restrictive diets are stopped and calorific intake increases. The Nutrition Practice Guideline (NPG) sets out an individualized exercise plan for diabetes. This guideline suggests aiming for >150 min/week of moderate-intensity (50–70% maximum heart rate) aerobic physical activity, divided between 3 days per week, and with no gap of more than two consecutive days without exercise.[269] Daily physical activity is known to be an essential component of long-term weight control.[270]

It should come as no surprise to practitioners that there are many forms of exercise that can be prescribed. Numerous studies confirm that all kinds of physical activity and exercise results in immediate improvements in glycemic control. However, the types of exercise that appear most beneficial for reducing post-prandial glycaemia and insulin resistance appear to be pre-prandial resistance training and high-intensity interval exercise.[270,271] Interestingly, some authors have conceded that prescribing voluntary exercise successfully is fraught for the majority of diabetic patients and that a completely different approach to prescription exercise in the sedentary needs to be taken. These authors have suggested that neuromuscular electrical stimulation (NMES) devices can deliver exercise in a sedentary population crucially

without requiring any substantial patient movement at equivalent (or even faster) rates to voluntary aerobic exercise. A fit or obese person using an NMES system while watching television for 6 hours could burn over 2000 kcal - an impressive addition to non-exercise activity thermogenesis (NEAT). NMES devices are already widely used and available in rehabilitation and sports medicine for a range of indications. Exercising with NMES systems appears to improve both the strength as well as aerobic capacity of muscle – similar to vigorous voluntary exercise.[272] Another attraction of modern NMES devices is that they are able to exercise big muscle groups directly without loading any joints, and without the need for extensive back, hip or knee movements – as these joints are often painful or at risk in diabetics.-[272–278]

There is evidence that NMES can play an important role in controlling T2DM.[279] Studies of NMES devices in diabetics have shown improvements in HbA1c equivalent to, or better than, taking real exercise.[280] The average improvement in HbA1c of 0.8 ± 0.7% with NMES therapy is clinically significant and compares well with lifestyle intervention studies where an exercise effect of 0.62% improvement can be expected. Like most exercise modalities, improvement is seen even after short-term use.[281,282] Of particular interest, there may be unexpected metabolic advantages of using NMES for type 2 diabetes, over and above voluntary exercise. Kimura et al[283] have proposed the benefits of targeting type 2b muscle fibres in exercise for T2DM, as this is associated with a shift towards oxidative metabolism. NMES is thought to preferentially recruit these type 2b fibres when compared to voluntary exercise.[284,285] When using NMES, it appears that the muscle is preferentially metabolizing carbohydrate as a substrate. This has been reported in healthy subjects[273,286] but has also been noted in a small study with just nine obese patients.[280] Consistent with this observation is the finding of high lactate levels, up to 15.3 mmol/L in two studies on healthy volunteers.[273,287] Sola-Penna et al[288] argue that lactate is probably 'a regulatory molecule that modulates the integration of metabolism' including glucose.

Much further research is needed to elucidate the basic metabolic mechanisms and to optimize exercise prescription with NMES therapy for type 2 diabetes. Commercial, patient-friendly, personal use devices specifically for type 2 diabetes have yet to emerge, although Slendertone has launched evidence-based NMES belts for general personal wellness.[289] Practitioners working with type 2 diabetics need to keep abreast of advances in exercise science that could unlock the hugely beneficial role of exercise for an otherwise frequently sedentary population of patients.

Computer Modelling Reversal and Remission

Ha et al[290] have explored and extended a mathematical model of the pathogenesis, prevention, and reversal of T2DM first envisaged by Topp et al.[291] Simulations based on the model by Ha et al offer a mathematical explanation of how a moderate, gradual program of weight loss and exercise could be effective for preventing but not reversing diabetes, and diabetes of longer duration would be more difficult to reverse. Also, the model predicts that standard glucose-lowering drugs like metformin on their own could help with the prevention but never the reversal of established T2DM. On the other hand, acute caloric restrictions – whether via VLEDs or bariatric surgery – show immediate improvements in glycemic control, long before any weight loss, and are the interventions most likely to generate reversal and remission of T2DM. Further work on computer modelling would greatly assist clinical researchers, especially if it was possible to simulate whether interventions on their own or in novel combinations could reach the required threshold for remission.

Does Remission Translate into Better Long-Term Outcomes for T2DM Patients?

Whilst practitioners are still considering the many very positive results that upset the conventional wisdom and show T2DM to be reversible, the big questions for the future are how to convert reversal into a durable remission, and whether long-term remission can translate into the prevention of any (further) macrovascular, and more importantly, microvascular damage caused by the T2DM. Only long-term follow-up of patients in remission can unequivocally answer these questions.[292] Interestingly, from long-term studies of remission after bariatric surgery, some predictors of remission have already been identified. These include diabetes duration, degree of medication use, glycemic control, BMI, manifestation and severity of co-morbidities, C-peptide levels (lower levels being a proxy marker of poor endogenous insulin

production), and age.[293] Further focus and study into the heterogeneity of these predictors will help practitioners optimize and personalize the approach for each T2DM patient and provide a framework for targeting and personalizing more effective support for remission to take place in addition to making it more durable.

Conclusions and Recommendations for Further Study

Multiple, disparate therapeutic interventions (from dietary to surgical) confirm that T2DM patients can become normoglycemic again, and early results suggest that this reversal could be maintained in the long term. Just as we struggle to untangle the complex role of diet in the pathogenesis and prevention of T2DM,[294] we can postulate that, despite the variety of interventions, the underlying mechanisms of reversal in each therapeutic approach could have some pathway(s) in common – and some of these phenomena might be explained by the Taylor Twin Cycle Theory. This may seem paradoxical, because there is no obvious connection between, say, taking exercise and bariatric surgery, using orlistat or a GLP-1 agonist, but some shared underlying mechanisms or pathways should not come as a complete surprise. There is much underlying pathophysiological complexity, with many unknowns, but it is interesting that these widely disparate methods appear to boil down to metabolic interventions that can fix the pathophysiology from very different starting points. It is not yet known if the progression of macrovascular and microvascular disease in T2DM patients is prevented by long-term reversal or remission. Further studies are needed to address these points.

As the cost of diabetes has escalated, society can no longer afford to ignore the pandemic of lifestyle diseases, so understanding T2DM remission becomes more of a priority. Whereas the current standard of care still needs to be followed carefully, many practitioners might choose to promote reversal/remission to their patients based on the latest evidence. The current standard of care has done little to check the pandemic of diabetes. Therefore, this review has highlighted for the practitioner the various approaches to reversing T2DM. Table 4 summarizes some of those approaches.

The future is likely to present a stepwise approach to T2DM reversal and remission based on the patient's metabolic baseline and background profile. Combination therapy – including possibly multi-drug therapy – rather than monotherapy will be the key feature of successful reversal and remission. Remission will be seen as the primary aim especially for pre-diabetes and newly diagnosed T2DM patients, who are the two groups most likely to go into long-term remission with the least effort.

Remission-focused services for T2DM are an emerging area and not a part of routine diabetes care. Formal remission services may not be feasible until long-term studies elucidate the efficacy of different approaches and also their optimum combination. Consequently, the field is left to opportunistic evidence-based practice. There is little consensus and few guideline recommendations regarding the optimum timing, combination, and mode of delivery of intervention components to help people achieve T2DM remission. Researchers will surely need to test many combinations – for example, whether there is added value from a very low calorie diet that is low carb at the same time. Reversal can now be supported by scalable digital behavior change, and practitioners can then pick from multi-drug pharmacotherapy (with or without a bariatric intervention) in a personalized way in order to truly move the T2DM needle from reversal onto long-term remission. The fact that a personalized, multi-disciplinary, and combination, step-wise approach is required for reversing T2DM should come as no surprise – in the same way that oncology patients are managed with a carefully filtered, personalized mix of surgery, radiotherapy, and chemotherapy based on sensitive, specific evidence-based markers (wherever possible) of their baseline disease status, disease profile, and response.

Practitioners should therefore see the various different approaches to T2DM reversal as entirely complementary to each other with common mechanistic pathways. There is already a large volume of (unhelpfully competing) literature available regarding the various strategies, medications, and interventions for reversing T2DM when used alone, and sometimes when used in dual or triple combinations – and studies are already emerging that many of these approaches can be combined safely and effectively, with some data on patient selection.

Data on all the different permutations of multi-drug combinations with all the other strategies and their impact on weight loss and glycemic control are not available yet. But the evidence that triple drug therapy is much more efficacious than mono or dual therapy is already emerging. Only much further study can give practitioners the bigger picture. A truly rationalized approach to T2DM reversal will come when all the numerous permutations of intervention available are

Table 4 A Summary of the Most Promising Therapeutic Approaches for Reversing T2DM

Therapeutic Approach	Type	Pros	Cons
Surgery	Gastric Balloon	Rapid results	Usually needs procedure to remove; weight regain after removal
	Gastric Band	Rapid results	Minimally invasive; may need adjustment; weight regain after removal
	Sleeve gastrectomy/Gastric bypass	Most effective long-term intervention	Invasive (laparoscopic)
Dietary Intervention	VLEDs	Non-invasive	Weight regain in the long-term
	LCDs	Non-invasive	Weight regain in the long-term
Digital Behavior Change	Usually based on CBT techniques	Non-invasive, scalable, cheap	Weight regain in the long-term
Exercise	High Intensity Interval Training	Improves health in general	Requires good musculoskeletal and cardiorespiratory status
	Resistance Training	Improves health in general	Requires good musculoskeletal and cardiorespiratory status
	NMES	Can be used by sedentary or those with musculoskeletal and/or cardiorespiratory restrictions	Expensive to buy NMES equipment and consumables; commercial NMES models not yet optimized for diabesity
Pharmacotherapy	Short term intensive insulin therapy	Effective, if applied early	Needle phobia
	Orlistat ± metformin	Effective especially for prevention, if applied with low fat diet	GI side effects
	Orlistat ± metformin ± SGLT2 inhibitors ± GLP-1 agonists	Effective, if applied with low fat diet	Side effects increase with multidrug therapy
	Alpha-glucosidase inhibitors	Effective (miglitol > voglibose > acarbose)	GI side effects, must be taken at start of food
	Metformin + pioglitazone + gliclazide	Effective if used for long enough	Side effects increase with multidrug therapy
	Metformin + pioglitazone + repaglinide	Effective especially for newly diagnosed with T2DM	Side effects increase with multidrug therapy
	Metformin + pioglitazone + glibenclamide (for patients already on insulin)	Effective if used for those already on insulin	Side effects increase with multidrug therapy
	GLP-1 or GLP1/GIP agonists	Effective, especially at higher dose	Expensive

studied in detail, providing the evidence base for practitioners to optimally combine all these therapies in a stepwise fashion that is personalized to patient baselines and profiles. For now, practitioners will have to rely on the available evidence and to be open-eyed about the possibilities of achieving better outcomes for their type 2 diabetic patients with combination approaches and aiming for remission more often, and earlier in the course of the disease.

This paper captures some of the exciting details about the possibilities of reversing T2DM – a disease that has always been viewed as chronic and progressive. It has tried to pick up the available evidence and fill in gaps as much as possible

where guidelines fall silent. In particular, remission should be a treatment goal for those who are still pre-diabetic, newly diagnosed type 2 diabetics, and type 2 diabetics of less than 6 years duration – although that is not to rule out those who have had T2DM for longer – and practitioners should remember the main driver and predictor of long-term remission is weight loss of 15kg or more.[17,18,160,295]

The authors of this review paper propose that remission of T2DM should be the primary clinical goal in the management of T2DM. There is an abundance of options that have potential to effect T2DM remission, nearly all of which require weight loss. Although incurable, diabetes prevention, delay in onset, and reversal are real-world possibilities. When it comes to healthcare, one size does not fit all, and a mixture of different approaches and at different intensities is likely necessary to maximize remission rates. Patients will need to be offered a menu of options to choose from, and to be involved in this "mix and match" from the start. This review offers practitioners a practical, evidence-based approach in order for them to provide individualized care in a clinical setting on an informed basis. A lot more could be said about how to motivate people, society, and policy makers to understand the true impact of the diabesity pandemic. Prioritizing a wholesale change in our approach to T2DM is essential, because if the status quo is maintained, individuals, society at large, and our precious environment will pay an unacceptably high price.

Disclosure

Dr Mo Al-Qaisi reports involvement in the innovation start up Ziro Fibre Ltd, which is focused on diabesity reversal using functional appetite quenching drinks and digital behaviour change. The remaining authors report no conflicts of interest in this work.

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